Claims

1. Use of a Ciz 1 nucleotide or polypeptide sequence, or any fragment or variant thereof as a target for the identification of agents which modulate DNA replication.

2. A screening method for the identification of agents which modulate DNA replication wherein the screening method comprises the use of Ciz1 nucleotide or polypeptide sequence or any fragment or variant thereof.

3. The screening method according to claim 2 wherein said method comprises detecting or measuring the effect of an agent on a nucleic acid molecule selected from the groups consisting of:

a) a nucleic acid molecule comprising a nucleic acid sequence represented in any of Figures 14, 15, or 21;

b) a nucleic acid molecule which hybridises to the nucleic acid sequence in (a) and which has Ciz1 activity or activity of a variant thereof;

c) a nucleic acid molecule which has a nucleic acid sequence which is degenerate because of the genetic code to the sequences in a) and b) and a candidate agent to be tested;

d) a nucleic acid molecule derived from the genomic sequence at the Ciz1 locus or a nucleic acid molecule that hybridises to the genomic sequence.

4. The method according to claim 3 wherein said nucleic acid molecule is modified by deletion, substitution or addition of at least one nucleic acid residue of the nucleic acid sequence.

5. The screening method according to claim 2, wherein said method comprises one or more of the following steps:

(i) forming a preparation comprising a polypeptide molecule, or an active fragment thereof, encoded by a nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule comprising a nucleic acid sequence represented in any of Figures 14, 15, or 21;

b) a nucleic acid molecule which hybridizes to the nucleic acid sequence in (a) and which has Ciz1 activity or activity of a variant thereof;

c) a nucleic acid molecule which has a nucleic acid sequence which is degenerate because of the genetic code to the sequences in a) and b) and a candidate agent to be tested;

d) a nucleic acid molecule derived from the genomic sequence at the Ciz1 locus or a nucleic acid molecule that hybridises to the genomic sequence; and

(ii) detecting or measuring the effect of the agent on the activity of said polypeptide.

6. The method according to claim 5 wherein said polypeptide is modified by deletion, substitution or addition of at least one amino acid residue of the polypeptide sequence.

7. The method according to any of claims 3 to 6 wherein said screening method is a cell-based screening method.

8. The method according to claim 7 wherein the cell naturally expresses the Ciz1 polypeptide.

9. The method according to claim 7 wherein the cell is transfected with a nucleic acid molecule encoding Ciz 1 or a fragment or variant thereof.

10. An agent identified by the method of any of claims 1 to 9.

11. An agent according to claim 10 wherein said agent is an antagonist of Ciz1 mediated DNA replication.

12. An agent according to claim 10 wherein said agent is an agonist of Ciz1 mediated DNA replication.

13. An agent according to any of claims 10 to 12 wherein said agent is selected from the group consisting of: polypeptide or nucleic acid probe; polypeptide; peptide; aptamer; chemical; antibody; nucleic acid.

13. An agent according to claim 12 wherein said agent is an antibody molecule and binds to any of the sequences represented by Figures 16, 17, or 20.

14. An agent according to claim 12 wherein said agent is an anti-sense nucleic acid molecule or RNAi which binds to and thereby blocks or inactivates the mRNA sequence of Ciz1 or any variant thereof.

15. An agent according to claim 14 wherein said agent binds to any part of the sequences illustrated in Figures 14, 15, or 21 or in part (i) b-d of claim 3.

16. A vector as a delivery means for delivering an antisense or an RNAi molecule to a cell.

17. A vector according to claim 16 wherein the vector includes an expression cassette comprising the nucleotide sequence selected from the group consisting of;

a) the nucleic acid sequence which encodes Ciz1 amino acid sequence as shown in Figs 14, 15, and 21.

b) a nucleic acid molecule which hybridizes to the nucleic acid sequence of (a) ;

c) a nucleic acid molecule which has a nucleic acid sequence which is degenerate because of the genetic code to the sequences in a) and b) and any sequence which is complimentary to any of the above sequences;

d) a nucleic acid sequence that encodes Ciz1 pre-mRNA (i.e., the genomic sequence),

18. A vector according to claim 17 wherein the expression cassette is transcriptionally linked to a promoter sequence.

19. A diagnostic method for the identification of proliferative disorders comprising detecting the presence or expression of the Ciz 1 gene, Ciz1 splice variants and mutations in the genomic or protein sequence thereof.

20. A diagnostic method according to claim 19 wherein said method comprises one of more of the following steps:

(i) contacting a sample isolated from a subject to be tested with an agent which specifically binds a polypeptide with Ciz 1 activity or a nucleic acid molecule encoding a polypeptide with Ciz 1 activity; and

(ii) detecting or measuring the binding of the agent on said polypeptide or nucleic acid in said sample;

(iii) use of reverse-transcribed PCR or real-time PCR to monitor Ciz1 and Ciz1 isoform expression and to measure expression levels.

(iv) measuring the presence of nucleic acid or amino-acid mutations based on altered conformational properties of the molecule.

21. Use of an agent identified by the method of any of claims 1 to 9 in association with a pharmaceutically acceptable carrier, excipient or diluent, as a pharmaceutical.

22. Use of an agent identified by the method of any of claims 1 to 9 for the manufacture of a medicament for use in the treatment of proliferative disease.

23. Use according to claim 22 wherein said proliferative disease is cancer.

24. Use according to claim 23 wherein said cancer is a paediatric cancer and is selected from the group consisting of; retinoblastoma, neuroblastoma, Burkitt lymphoma, medulloblastoma, Ewings Sarcoma family tumours (ESFTs),

25. Use according to claim 23 wherein the cancer is a carcinoma, adenocarcinoma, lymphoma or leukemia.

26. Use according to claim 22 wherein the disease is liver, lung or skin cancer or metastasis.

27. A method to treat a proliferative disease comprising administering to an animal, an agent identified by the method of any of claims 1 to 9.

28. Use of an agent identified by the method of any of claims 1 to 9 for the manufacture of a medicament to slow cell division or growth.

29. A kit comprising a diagnostic, prognostic or therapeutic agent identified by the method of any of claims 1 to 9.